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Severe respiratory disease and its relationship with respiratory viruses in Colombia

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Summary
Background: There are important gaps in our understanding of the epidemiology of respiratory virus infections in tropical countries. In September 2003, the Colombian epidemiological surveillance system was notified of several deaths from an acute respiratory disease (ARD).
Methods: In order to identify the agents associated with ARD cases, a clinical and laboratory-based surveillance system was implemented throughout the country.
Results: Between September 19 and December 31, 2003, 64 suspected cases of ARD were reported; of these reported cases, 21 (33%) died. Among 25 patients who underwent virus studies, influenza A (H3N2) ($n = 7$) was the most frequently identified agent. Other viruses included parainfluenza (4), influenza B (1), and respiratory syncytial virus (3). The peak occurrence of cases and deaths coincided with the replacement of the influenza A (H3N2) Panama strain, which had been circulating in Colombia since 1999, by three new influenza A (H3N2) strains (Korea, Fujian, and Wyoming).
Conclusions: This outbreak led to the strengthening of surveillance for respiratory viruses and to new national recommendations for influenza vaccination in Colombia.

Introduction

The Colombian National Institute of Health (CNIH) has conducted a laboratory-based surveillance system for respiratory viruses (RV) since 1997. More than 2905 samples from suspected cases of acute respiratory disease (ARD) were submitted for viral diagnosis between 1997 and 2002. Respiratory syncytial viruses were the most frequent isolates (61%) associated with respiratory syndromes, followed by influenza virus (23%), adenovirus (5%), and parainfluenza viruses 1, 2, and 3 (5%).[1,2]

In temperate countries, the winter season is associated with an increase in hospitalization rates for respiratory diseases as well as with an increased risk of clinical complications among patients with chronic diseases or among children under two years of age, most of whom have no underlying diseases.[3] However, in Colombia and other South American and tropical countries there are still important gaps in the

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understanding of the disease burden imposed by respiratory viruses.[4–6]

In September 2003, the CNIH received reports of several deaths among patients who had sought medical care for a severe ARD. In order to determine whether these deaths were related to influenza virus or other respiratory agents, an epidemiological alert was sent to the district health secretaries throughout the country with the aim of identifying other cases of ARD. An additional goal of this initiative was to improve the quality of the clinical and microbiological investigation of individual cases and to implement a more organized public health response to this and similar threats.

Methods

The national health system in Colombia is divided in 36 health districts. All of them were requested to notify the CNIH of any increase in the number of patients with ARD. Each district was also asked to pay special attention to adult patients with severe ARD of short duration and to report these cases to the CNIH.

The recommended definition for a suspected case of severe ARD was a patient with fever and cough who developed a severe respiratory illness (high respiratory rate for age, intercostal retractions, cyanosis) or any patient dying with multi-lobar pneumonia or ARD of less than 10 days duration. It was recommended that each suspected case should be studied with a complete blood count, chest X-ray, blood culture, and nasopharyngeal swab for virus isolation. Medical officers were told that patients meeting these criteria should be sent for further treatment to hospitals with the highest level of medical technology available in the area. When a suspected case was identified, local epidemiologists were encouraged to complete an epidemiological surveillance form and send it immediately to the CNIH by fax or e-mail, and to promptly submit nasopharyngeal samples. The clinical and epidemiological information collected from patients included demographic data (age, sex, city of residence), clinical data (cough, respiratory distress, headache, gastrointestinal symptoms, underlying diseases), clinical diagnosis, duration of illness, clinical management, presence of clinical complications, and patient status (alive or dead) when discharged from hospital.

Specimens from the upper respiratory tract were obtained with nasopharyngeal swabs, while samples from the lower respiratory tract were obtained using bronchial washings. All samples were refrigerated (4 °C) and sent to the CNIH virology laboratory. For fatal cases, histological and pathological specimens were obtained from lung, trachea, heart, brain, liver, and kidney. Organ samples were preserved in paraffin or formaldehyde and sent to the pathology laboratory at the CNIH.

Respiratory samples from suspected ARD patients were tested for viruses using Madin–Darby canine kidney tissue cell cultures. If the presence of influenza virus was suggested by occurrence of a cytopathic effect, the isolate was identified by hemagglutination inhibition (HAI) using the World Health Organization (WHO) influenza reagent kit.[7] Indirect immunofluorescence (Light Diagnostics, Chemicon) was used to identify other respiratory viruses.[8] All laboratory work was carried out in the virology laboratory of the National Institute of Health in Bogotá. Quality control and strain identification were done by the influenza branch of the CDC in Atlanta, GA, USA.

Data were stored in an EpiInfo 6.04 database and statistical analyses of the epidemiological and clinical variables were conducted using EpiInfo 3.3.2. We calculated the case fatality rate (CFR, %) by age, gender, underlying disease, and for viral agents when possible.

Results

Between September 19 and December 31, 2003, 64 suspected cases of severe ARD were reported to the CNIH; of these reported cases, 21 died (CFR = 33%). Cases were reported from five of the 36 health districts, and most reports came from the central area of the country. The peak period for case reports was the six weeks from October 15 through November 30. Most of the 21 fatal cases occurred during the first week of November. Of these, 16 died within seven days of the onset of illness (Figure 1 and Table 1).

Severe ARD occurred in all age groups, but most cases were concentrated in the group aged 15 to 44 years (n = 22, 34%), followed by those in the group aged 45 to 74 years (n = 15, 23%). The highest case fatality rate (50%) was observed among those aged 15 to 44 years. Cases were evenly divided among men and women (32 each), but deaths were more common among women (14) than men (7) (Table 2).

Overall, the most common symptoms were cough (81%), fever (78%), asthenia (78%), body pain (78%), and chest pain (11%). Among patients who died, fever was the most frequent symptom reported (17), followed by cough (16) and chest pain (8).

Nine (14%) of 64 patients had underlying medical conditions. Chronic respiratory disease (3) and high blood pressure (3) were the most frequent diseases reported, followed by ventricular–peritoneal shunt (1), active pulmonary tuberculosis (1), and coagulation disorder (1). Five out of nine cases with underlying diseases died (CFR = 56%).

In 20 cases, accurate information was obtained on the chest radiographs. The most frequently diagnosed pattern was diffuse infiltrates (12) followed by multi-lobar pneumonia (2), pneumothorax (1), diffuse opacity (1), and increased bronchial markings (1). Three cases had normal chest radiographs. Among the 21 fatal cases, chest radiographs were available for ten. In this group, lung infiltrates were most frequently observed (8), followed by multi-lobar pneumonia (1) and a normal radiographic pattern (1).

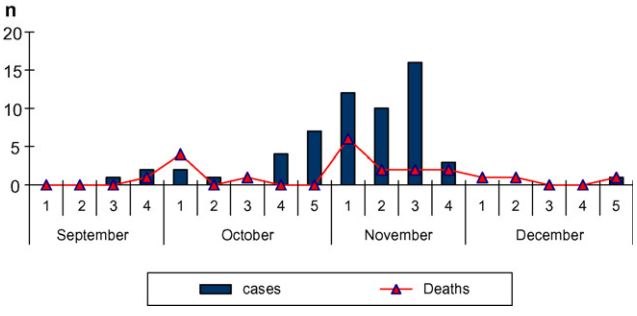

Figure 1 Weekly distribution of acute respiratory disease cases and deaths, September through December 2003; Colombia.

Table 1 Distribution of deaths by age group and days of illness

Days of illness	Age groups (years)					Total *n*	Total %
	<1	1–14	15–44	45–74	≥75		
0–3	1	0	2	1	2	6	28.6
4–7	0	2	5	3	0	10	47.6
8–11	0	0	2	0	0	2	9.5
12–15	0	0	0	0	0	0	0
16–19	0	0	2	1	0	3	14.3
Total	1	2	11	5	2	21	100

Local health services were able to collect adequate nasopharyngeal samples in 25 (39%) of the 64 cases. Using indirect immunofluorescence, 13 of the 25 cases were virus-positive. The most frequent virus found was influenza A (H3N2) (7), followed by parainfluenza (4), respiratory syncytial virus (3), and influenza B (1). In two cases, parainfluenza 1 was associated with respiratory syncytial virus. Attempts were made to identify respiratory viruses in eight (38%) of the 21 fatal cases. Influenza A (H3N2) viruses were identified in three cases, and the strains involved were Korea in two cases and Wyoming in one. Influenza B and parainfluenza viruses were identified in one case each. Three cases were negative for respiratory viruses.

Table 2 Distribution of acute respiratory disease and deaths by age, sex, geographic area, and virological diagnosis

	Deaths	Cases	Case fatality ratio %
Age group (years)			
<1	1	2	50
1–14	2	10	20
15–44	11	22	50
45–74	5	15	33
≥75	2	13	15
No data	0	2	0
Total	21	64	33
Sex			
Female	14	32	44
Male	7	32	22
Total	21	64	33
Geographic area			
Antioquia	6	21	28
Bogotá	4	5	80
Caquetá	1	1	100
Cundinamarca	5	23	22
Norte de Santander	5	14	36
Total	21	64	33
Virus			
Influenza A H3N2	3	7	43
Influenza B	1	1	100
Parainfluenza 1	1	2	50
Parainfluenza 1 + RSV	0	2	0
RSV	0	1	0
Negative	3	17	18
Total	8	32	25

RSV, respiratory syncytial virus.

Overall, clinical management included antimicrobial treatment for 21 (35%) of 60 cases. Among the 21 cases that died, only four (19%) received antibiotics. A post-mortem examination was obtained for 10 of the 21 fatal cases. The most frequent finding was bacterial pneumonia (6), followed by interstitial pneumonitis (2) and diffuse alveolar damage (2). *Staphylococcus aureus* was identified as the associated agent in one case who died of bacterial pneumonia. No further bacterial agent was isolated.

Discussion

The data in this report were obtained from a surveillance system that was rapidly implemented during an outbreak of severe ARD in a developing country. Pneumonia and influenza are not systematically reported by the weekly surveillance and epidemic alert system in Colombia, and therefore data came mainly from areas with better surveillance systems such as those in Bogotá, Antioquia, and Cundinamarca. These regions represent about 20% of the Colombian population. Less developed health districts were less able to provide timely notification of cases.

Despite its shortcomings, this study provided Colombian health officials with an initial estimate of the importance of respiratory viruses as causal agents of severe ARD. For the first time in 7 years, they were able to link information from the sentinel surveillance system for respiratory viruses with individual reports of severe ARD. Although data came from only five of Colombia's 36 health districts, they documented that influenza viruses were circulating simultaneously in several regions throughout the country. The data also suggested that simultaneous circulation of several strains of influenza A H3N2 virus (Panama, Korea, and Fujian serotypes) could have been one of the reasons why severe cases were more frequently reported during the influenza season. Results from the surveillance network had earlier indicated that influenza A (H3N2) Panama was the dominant strain that circulated from June 1999 to September 2003, when it was replaced by influenza A (H3N2) Fujian, Korea, and Wyoming strains. As shown in Figure 2, the temporal peak of severe cases and deaths coincided with the increase in circulation of several strains of influenza A (H3N2) virus.

We were unable to compare the occurrences of similar cases for preceding years since this was the first time that such surveillance was implemented in the country. However, we looked back at the overall mortality due to respiratory

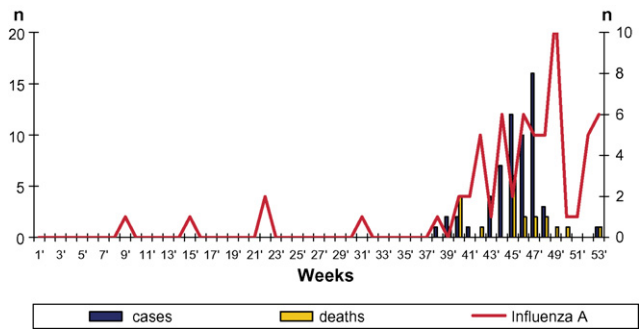

Figure 2 Weekly distribution of acute respiratory disease cases, deaths, and influenza virus isolates, 2003; Colombia.

diseases reported between years 2000 and 2004 for the period between September and December in Bogotá and Cundinamarca, which were the areas reporting more cases in this study. We found a 33% increase in deaths related to respiratory causes during 2003, compared with the median for the five years (1019 deaths vs. 819). This suggests that there has been an overall increase in mortality that could be due to the change observed in the strain of influenza virus.[9]

Similar to reports of other studies,[3,6,7,10] our data confirmed that people with underlying chronic diseases, especially cardiopulmonary conditions, were at highest risk of death during influenza seasons. This finding is not widely known in tropical countries where surveillance systems for respiratory viruses are weaker than those in more temperate countries. The lack of a governmental vaccination policy was another factor that could have contributed to the influenza-related mortality of high-risk individuals. Prior to 2004, only people who could pay for influenza vaccine were vaccinated, and coverage rates were very low. However, in 2005 and 2006, health officials added influenza vaccination for people older than 65 years and children under two years of age to the national immunization program.

Colombian health officials have learned several lessons from this experience. First, the laboratory network for influenza surveillance was strengthened, and more health departments acquired capabilities to isolate and characterize influenza viruses. Currently, 10 departments report weekly on the occurrence of suspected cases of influenza and the laboratory results of active surveillance. Second, influenza vaccination is now an integral part of the national immunization program targeting children under two years of age, adults over 65 years, and people with risk factors for severe influenza-related disease.[11] Finally, Colombia has launched a program to strengthen its hospital networks in order to be more prepared to deliver adequate medical care to people suffering from ARD. The lessons learned from this experience are relevant to other tropical and developing countries.

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Conflict of interest: No conflict of interest to declare.

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